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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/713,268	11/17/2003	Serengulam V. Govindan	018733-1317	1475

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EXAMINER	
CELSA, BENNETT M	
ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 03/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/713,268	GOVINDAN, SERENGULAM V.	
	Examiner	Art Unit	
	Bennett Celsa	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-20 and 23-32* is/are pending in the application.

4a) Of the above claim(s) *14,15,26 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-13,16-20,23-25 and 28-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/03;11/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 11-20 and 23-32 are currently pending.

Claims 14-15 and 26-27 are withdrawn from consideration.

Claims 11-13, 16-20, 23-25, and 28-32 are under consideration.

Election/Restrictions

1. Upon further consideration, the restriction between Groups I-III is hereby withdrawn and an election of species among the three (3) groups is hereby substituted therefore; with the ultimate election of species retained.

2. Applicant's election with traverse of Group I (claims 11-20 and 23-32 in part) and the election of MCC-Gly-D-Tyr-D-Lys-(melibiose)-OH where MCC is 4-N-maleimidomethyl-cyclohexane-1-carbonyl in the reply filed on 12/22/04 is acknowledged. Applicant's arguments regarding restriction are rendered moot. Regarding the election of species requirement applicant argues that it is not burdensome to search the different inventive species since they are commonly classified (e.g. 530/345) and posess structural similarity (e.g. of lys/orn/arg). This is not found persuasive for the reasons already recited in the restriction/election requirement e.g. burdensome manual/computer searches requiring different sequence/structure/bibliographic searches in literature and patent art areas.

The requirement, as modified is still deemed proper and is therefore made FINAL.

3. It is noted that applicant's response was incomplete in that applicant failed to indicate the claims readable on the elected invention. In order to expedite prosecution (e.g. by not sending out a non-responsive communication) it would appear that the elected invention reads on claims 11-13, 16-20, 23-25, and 28-32.

4. Claims 14-15 and 26-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

Priority (Intervening Reference)

5. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The present application (10/713,268: filed 11/17/03) claims 35 USC 120 priority:

a. as a divisional of 09/605,873 (filed 6/29/00);

b. which is a CIP of 08/919,477 (filed 8/28/97)

CIP of PCT/US97/23711 (filed 12/19/1997)

CIP of PCT/US97/14998 (filed 8/27/97).

Present claims 11-32 (including the election invention: claims 11-13, 16-20, 23-25, and 28-32) are entitled to 35 USC 120 to the date of filing of the 09/605,873 application (6/29/00).

However, NEW MATTER present in the present application which is necessary for both descriptive and enablement support i.e.

- (see present specification page 7, line 20-28 (6^{th} embodiment presently claimed);
- page 10, line 23- page 11, line 21: improvement over DLT-embodiments of products synthesized by the presently claimed invention); and
- Example 16 (illustrating present syntheses and resulting compound)

Which is NOT present in the prior application recited in item B results in the DENIAL OF 35 USC 120 PRIORITY of the present claimed to the filing date of the applications recited in item b for failure to satisfy 35 USC 112/1.

Accordingly, for purposes of prior art, the present claimed invention is afforded the filing date of the immediate parent application (item a. above) e.g. 6/29/00.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 11-13, 16-20, 23-25, and 28-32 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 11 and 23 (and claims dependent thereon) are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: the attachment point of the "linking group" to the "carbohydrate-appended peptide".

b. In claim 23 (and claims dependent thereon), the phrases "the carboxy terminus is ... , D-arginine or D-ornithine" and "the side chain of D-arginine or D-ornithine" lacks antecedent basis since the claim prior recites that "a carboxy terminus (is) formed from a D-lysine" NOT D-Arg or D-Orn.

c. Claim 25, which is dependent on claim 11, lacks antecedent basis for "the side chain of D-arginine or D-ornithine".

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 11-13, 16-18, 23-25, and 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Strobel et al. Archives of Biochemistry and Physics, Vol. 240, No. 2 (Aug. 1985) pages 635-645 and Govindan et al., Bioconjugate Chem. Vol. 10 (2/99) pages 231-240.

The presently claimed invention is drawn to a method for producing a carbohydrate (CHO)-appended peptide useful for radioiodinating an antibody, comprising conjugating a radioioditinable peptide to a CHO to form a CHO-appended peptide; wherein the CHO-appended peptide comprises

(a) a peptide that comprises at least one D-tyrosine, an amino terminus, a carboxy terminus formed from a D-lysine and no contiguous L-amino acids between the D-tyr and the carboxy terminus,

(b) a reducing CHO conjugated to the peptide via an ε-amino group of the D-lysine to form a CHO-appended peptide; and

(C) a linker group covalently binding said CHO-appended peptide to an antibody.

Thus, the presently claimed invention encompasses the reaction of: (LINKER) - Gly-D-Tyr-D-Lys which is reductively coupled to a "reducing CHO" utilizing the side-chain of an ε-amino group of the D-lysine.

Product embodiments include:

MCC-Gly-D-Tyr-D-Lys-(dilactitol/melibiose)-OH;

Where the elected linker is MCC (4-N-maleimidomethyl-cyclohexane-1-carbonyl); and the elected CHO is melibiose .

The Strobel et al. reference teaches a method of producing Iodinated glycoconjugate labels comprising conjugating a radioiodinatable amino acid (e.g. Tyrosine or tyramine) with a "reducing CHO" (e.g. dilactitol) with the presence of a linking moiety to a protein (e.g. antibody) present on the CHO or attached via the sidechain of the tyr or tyramine compound. SEE figure 2. The Strobel reference teaches that the protein (e.g. antibody) is coupled (e.g. to the CHO) via reductive amination but notes that "The ε-amino group of lysine residues is the likely site of attachment of glycoconjugates to protein by either coupling techinique" (page 640, left column).

The Strobel et al. reference method for making a I-glycoconjugate labels (E.g. dilactitol-I^{125} tyr/tyramine: DLT, when the amino acid is tyramine) differ from that presently claimed by replacing the Tyr or tyramine portion of the Strobel conjugate with a peptide containing D-amino acids and an antibody linker e.g. (MCC)-Gly-Dtyr-Dlys.

However, the Govindan et al. reference teaches that the Strobel et al. residualizing glycoconjugate labels (e.g. DLT: see reference 7 cited in the Govindan reference on page 231, right column) are problematic (e.g. low radioiodine incorporation into antibodies resulting in low specific activities and a mutistep antibody labeling procedure: see page 232, left column). In this regard, the Govindan reference teaches that utilizing a D-amino acid containing peptide comprising D-tyr (for iodination) and D-Lys (for ε-amino group coupling) and an amino terminal glycine attached to a linker (e.g. maleimide linker for antibody attachment) results in an improved residualized label. In this respect: the presence of D-amino acids renders the peptide bonds less

susceptible to the action of proteases in the lysosomes; with the N-terminal gly providing a means for coupling antibody. See e.g. Govindan at page 232, left column; abstract. More specifically, scheme 1, compound V is drawn to a thiolated MCC-Gly-Dtyr-Dlys.

One of ordinary skill in the art at the time of applicant's invention would be motivated to substitute the Linker-D amino acid containing Govindan peptide for Tyr/tyramine amino acid in the Strobel et al. reference conjugate and arrive at a method and product (e.g. MCC-Gly-D-Tyr-D-Lys-(dilactitol)-OH) which is within the scope of the presently claimed invention since:

a. the Govindan and Strobel references are immediately combinable since the Strobel reference is cited by the analogous Govindan reference providing an explicit reference motivation to combine the teachings of both references;

b. one of ordinary skill would be motivated to substitute the Govindan D-amino acid containing linker containing peptide for the Tyr or tyramine present in the Strobel DLT compound since the Govindan reference identifies the problems of the Strobel DLT compound (e.g. low radioiodine incorporation into antibodies resulting in low specific activities and a mutistep antibody labeling procedure: see page 232, left column) and arrives at a solution e.g. utilizing D-amino acids to increase specific activity (e.g. less enzymatic degradation) and attach the antibody linker using a Gly-maleimide derivative thus permitting easier (e.g. less steps) antibody labeling.

c. The Strobel reference further recognizes the use of reductive coupling using the ε-amino group side chain of lysine; which was incorporated in the Govindan peptide to

permit thiolation but which would be useful for CHO attachment as recognized by Strobel and as utilized in the presently claimed invention.

Thus it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to modify the Strobel reference method to substitute the Govindan D-amino acid containing peptide with N-terminl Gly-linker (e.g. MCC-Gly-D-Tyr-D-Lys) for the Strobel amino acid tyr/tyramine for coupling to the Strobel reducing CHO (e.g. dilactitol) and arrive at the presently claimed method with a reasonable expectation of success of attaining a more residual/stable/entrapped glycoconjugate label (E.g. D-amino acids result in a more enzymatically stable label) with the further benefit of more efficient antibody labeling. fig. 2).

10. Claims 11-13, 16-20, 23-25, and 28-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Strobel and Govindan (Bioconjugate) references as applied to claims 11-13, 16-18, 23-25, and 28-30 above, and further in view of Govindan WO 99/11294 (3/99).

The combined teaching of the Strobel and Govindan (Bioconjugate) references in the above 35 USC 103 rejection is hereby incorporated by reference in its entirety.

The combined Strobel/Govindan (Bioconjugate) reference method teaching differs from the presently claimed invention (e.g. claims 19-20 and 31-32) by choosing melibiose instead of lactose (e.g. dilactitol) as the reducing CHO to be conjugated to the amino acid or peptide.

However, Govindan WO 99 teaches the advantages of substituting melibiose for lactose utilized by Strobel e.g. in order to lessen aggregate formation and/or promote

oxidation by galactose oxidases. See e.g. pages 5-6 (background citing Strobel) ; page 7; and pages14-15.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to substitute melibiose for lactose in the combined method teaching of Strobel/Govindan (Bioconjugate) in order to optimize the glycoconjugate method and/or obtain more optimum glycoconjugate labels (e.g. to lessen aggregate formation and/or promote oxidation by galactose oxidases) with a reasonable expectation of success.

Relevant Prior Art:

1. Franano et al., Nuclear Medicine and Biology (1994) Vol. 21(8) pages 1023-34: teach labeled DTPA-ε-lysine as the primary lysosome excretory product.

Future Correspondences:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bennett Celsa
Primary Examiner
Art Unit 1639

BC
March 3, 2005